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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/758,291 | 01/14/2004 | Alexei Brooun | SYR-MVAS-5001-C1 | 5544 |

32793 7590 07/24/2006

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| EXAMINER | |
|---|---|
| NASHED, NASHAAT T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1656 | |

DATE MAILED: 07/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/758,291 | BROOUN ET AL. | |
| | Examiner | Art Unit | |
| | Nashaat T. Nashed, Ph. D. | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-7,10-13,16,17 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *17 and 19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed, June 26, 2006. Accordingly, claims 2, 3, 8, 9, 14, 15, and 18 have been canceled, and claims 1, 10-13, 17, and 19-23 have been amended.

Applicant's election with traverse of Group I, claims 1-16, in the reply filed on June 26, 2006 is acknowledged. The traversal is on the ground(s) that the amendment to claims 17-23 obviates the restriction requirements. This is not found persuasive because the inventions of Group II and I are related as a product and a method of its use. The restriction between a product and method of its use is proper since the crystal of Group I can be used in other methods such as in a method to purify the polypeptide of SEQ ID NO: 1.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17 and 19-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention II, there being no allowable generic or linking claim.

Claims 1, 4-7, 10-13, and 16 are under consideration in this Office action.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Crystallization of 3-Hydroxy-methylglutaryl Synthase.

The abstract of the disclosure is objected to because it does not describe the claimed invention. The abbreviation "MvaS" is not well-known in the art and it is defined only in the specification. The abstract should describe should describe the general teaching of the specification without the need to read the specification. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example paragraph 179, lines 5 and 6 at page 46. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The disclosure is objected to because of the following informalities:

(a) The pSX26 vector is presumed to be a commercial product. If this presumption is correct, the commercial source of said vector must be included.

(b) The abbreviations "TCEP" in paragraph 179 at page 46, and "IMAC" line 4 at page 47 are not defined in the specification. They must be defined at least once i the specification.

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the specification refers to a specific MvaS protein, the protein name must be accompanied by SEQ ID NO: 1 (see for example see Figures description of Figures 3-5 starting at page 11, paragraph 54, lines 2 and 4, at page 13, and the headings for Tables 2-4.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-7, 10-13, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4, 7, 10, and 13 are directed to all possible crystals of the protein consisting of SEQ ID NO: 1 with or without any compound bound to said protein and any method of making said crystal. Claims 5 and 11 limit the crystal of claim 1 and the method of claim 7 to any crystal of SEQ ID NO: 1 in space group $P2_12_12_1$; and claims 6 and 12 limit the crystal of claim 1 and the method of claim 7 to the a crystal having the unit cell dimension in the claims. Claim 16 is directed to any composition comprising a protein consisting of SEQ ID NO: 1 including any crystal in any space group and any unit cell dimension. The specification, however, only provides a single representative species of these crystals containing 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) bound to the protein of SEQ ID NO: 1 grown under the specific crystallization condition in paragraph 181 at page 47 in space group $P2_12_12_1$ having unite cell dimension a = 68.7, b=79.6, and c=150.2 Angstroms, $\alpha=\beta=\gamma=90$ degrees, see example 2 at page 47.

The court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] name chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." UC California v. Eli Lilly (43 USPQ2d 1398). For claims drawn to genus, MPEP section 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Also, MPEP section 2163 states that a representative number of species mean that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. At the time of invention, the protein from *Entrococcus faecalis* was known in the prior art, see for example Wilding *et al.* (J. Bacteriol. 2000, 182, 4319-4327). In general, for a species of crystal to be adequately and structurally described, the following must

be adequately described: (i) the exact chemical composition of the crystal, i.e., the structure feature of all molecules in the crystal including the amino acid sequence of any protein or nucleic acid, (ii) the space group of the crystal; and (iii) the unit cell dimension of the crystal. The prior art does not describe a crystal or the crystallization of the 391 amino acid residues of SEQ ID NO: 1 with or without a ligand. Thus, the specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the crystal obtained described in the previous paragraph. Similarly, the specification does not describe any other method to crystallize the protein of SEQ ID NO: 1, which produces a crystal suitable for structure detemination by X-ray crystallography. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1, 4-7, 10-13, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all-possible crystals comprising the amino acid the protein of SEQ ID NO: 1 and ay method of obtaining said crystal. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any possible crystals comprising the amino acid the amino acid sequence of SEQ ID NO: 1 and any method of obtaining said crystal. The specification provides guidance and examples in the form of an assay to obtain the protein of SEQ ID NO: 1 and obtain crystal comprising HMG-CoA bound to said protein under specific crystallization conditions (see example 1 and 2). While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to HMG-CoA synthase are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a crystal form is highly unpredictable without any clear expectation of success, and any change in a given crystallization condition including any minor alteration could alter the crystal form and its diffraction characteristics or even lack of crystal formation. It is now evident that protein

crystallization is the major hurdle in protein structure determination. For this reason, protein crystallization has become a research subject in and of itself, and is not simply an extension of structure biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with protein crystals. See for example, Gilliland *et* al, (*Curr. Open in Struct. Biol.* 1996, 6, 595-603) in particular page 600, left column second paragraph; Ke *et al.* (Methods, 2004, 34, 408-414); and Wiencek, J. M. (Ann. Rev. Biomed. Eng. 1999, 1, 505-534). Thus, the skilled artesian would be expected to screen large number of crystallization conditions, which may include screening variety of conditions in space, a micro gravity environment. Even if a crystal is obtained, it may or may not be suitable for structure determination by X-ray crystallography. Thus, searching for a crystallization conditions for a protein with or without ligand that is suitable for X-ray crystallography is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. The amount of experimentation to identify a crystal for the protein of SEQ ID NO: 1 that is suitable for structure determination X-ray crystallography is enormous. Since routine experimentation in the art does not include screening large number of crystallization conditions, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the chemical structure of a ligand(s) which is binds to SEQ ID NO: 1 and form the binary complex to be crystallized, and identify the exact crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paulsen *et al.* (Science 2003, 299, 2071-2074) in view of EMBL accession number Q835L4, Wilding *et al.* (J. Bacteriol. 2000, 182, 4319-4327) and Ford *et al.* (Protein Expr. Purif. 1991, 2, 95-107).

Paulsen *et al.* teach the nucleic and amino acid sequences of all genes of the vanocomycin-resistant *Enterococcus faecalis*, the abstract.

EMBL accession number Q835L4 teach the amino acid sequence of HMG-CoA synthase reported by Paulsen *et al.*

Wilding *et al.* teach the cloning of the genes involved in the biosynthesis of isopentyl diphosphate through the mevalonate pathway in gram-positive Cocci including HMG-CoA synthase from *E. faecalis*, see Figure 2 at page 5322. Also, they teach that low G+C gram-positive bacteria are major pathogen, see the first paragraph of the discussion at page 4323, and that all five genes encoding enzymes of the mevalonate pathway are essential for the growth of *S. pneumonial*, and inhibitor of HMG-CoA synthase are predicted to have a bacteriostatic effects.

Ford *et al.* is a review article for the use of fusion tags such as the His-Tag for the recovery and purification of recombinant protein, see in particular section 7 at page 100.

Claim 6 is directed to a fusion protein consisting of the amino acid sequence of EMBL accession number Q835L4 fused to the well-known cleavable KGHHHHHH tag at the C-terminus. Wilding *et al.* provide one of ordinary skill in the art with motivation to develop a method to make HMG-CoA synthase in large quantity to identify inhibitors that combat the pathogenic gram-positive Cocci bacteria. Further, the ordinary skill in the art would be motivated to make HMG-CoA taught in the EMBL accession number as it is obtained from antibiotic resistant bacterium. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to the nucleic acid encoding HMG-CoA synthase taught by Paulsen *et al.* inserted to one of the many commercially available vectors comprising the nucleic acid sequence encoding the His-tag, transform a host cell with said vector, express the protein and purify it on a Ni-affinity column to purify and isolate the protein. It should be noted that the His-tag can be either fused to the N-terminus or the C-terminus taught by Ford *et al.*, and that the His-tag may or may not be removed after the purification step, see Ford *et al.* page 102, left column. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656

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